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(54) **Use of Angiotensin-II antagonists in the treatment of hyperuricemia.**

(57) A pharmaceutical composition comprising a non-peptide type angiotension II receptor antagonist is useful for the treatment of hyperuricemia.

EP 0 480 659 A2

BACKGROUND OF THE INVENTION

It is considered that when uric acid content in blood exceeds a certain limit, uric acid would deposit as sodium urate and deposition of sodium urate on the articular cavity or kidney would cause gout, renal disorders or vascular disorders. As known causes of hyperuricemia, there are reduced excretion of uric acid, excessive production of uric acid, abnormality of purine metabolizing enzyme, disease associated with hematopoietic organ or renal disorders, administration of chemicals such as pyrazinamide or thiazide, and the like. Irrespective of any cause, continuous hyperuricemia results in incidence of gout in most cases and if further worsened, leads to renal insufficiency or cardiovascular disorders. Further in the case of children, a disease called Lesch-Nyhan syndrome which is caused by excessive production of uric acid due to enzyme abnormality is known.

Since these diseases are caused by high blood concentration of uric acid, drugs having an activity of excreting uric acid, for example, probenecid, sulfinpyrazone or benzbromarone have been used for the treatment of hyperuricemia.

The present invention provides compounds having excellent properties as agents for the treatment of hyperuricemia.

DETAILED DESCRIPTION OF THE INVENTION

As a result of extensive investigations to solve the foregoing problems, the present inventors have found that a series of non-peptide type compounds having an angiotension II receptor-antagonizing activity are useful for the prevention or treatment of hyperuricemia. The present invention has thus been accomplished.

That is, the present invention relates to compositions for the prevention or treatment of hyperuricemia comprising a non-peptide type compound having an angiotensin II receptor-antagonizing activity.

The non-peptide type angiotensin II receptor antagonists which are used in the present invention may be any compounds as long as they are compounds which do not fall under the category of compounds formed by binding two or more amino acids through peptide bond (-COHN-) and have an antagonizing activity against angiotensin II receptor. As non-peptide type compounds having such an action of antagonizing an angiotensin II receptor, compounds described in, for example, the following publications, may be given:

(a) Andrew T. Chiu et al.
The Journal of Pharmacology and Experimental Therapeutics, 247, 1-7 (1988)

(b) Andrew T. Chiu et al.
European Journal of Pharmacology, 157, 13-21 (1988)

(c) Andrew T. Chiu et al.
European Journal of Pharmacology, 170, 117-118 (1989)

(d) Pancras C. Wong et al.
Hypertenion, 13, 489-497 (1989)

(e) Andrew T. Chiu et al.
Biochemical and Biophysical Research Communications, 165, 196-203 (1989)

(f) Pancras C. Wong et al.
The Journal of Pharmacology and Experimental Therapeutics, 250, 515-522 (1989)

(g) Andrew T. Chiu et al.
The Journal of Pharmacology and Experimental Therapeutics, 250, 867-874 (1989)

(h) Andrew T. Chiu et al.
The Journal of Pharmacology and Experimental Therapeutics, 252, 711-718 (1990)

(i) John O. Koepke et al.
Hypertenion, 15, 841-847 (1990)

(j) Edwin K. Jackson et al.
Life Science, 46, 945-953 (1990)

(k) John V. Duncia et al.
Journal of Medical Chemistry, 33, 1312-1329 (1990)

(l) David J. Carini et al.
Journal of Medical Chemistry, 33, 1330-1336 (1990)

(m) Pancras C. Wong et al.

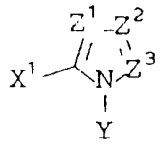
Hypertension, 15, 823-833 (1990)
(n) R. S. L. Chang et al.
Molecular Pharmacology, 29, 347-351 (1990)
(o) Alexander L. Johnson et al.
Drug News and Perspectives, 3, 337-351 (1990)

In addition, compounds disclosed in the following patents may also be given as examples of the non-peptide type compounds having an angiotensin II receptor-antagonizing activity which can be used in the present invention.

(1) Japanese Patent Application Laid-Open No. 54-148,788
(2) Japanese Patent Application Laid-Open No. 56-71,073
(3) Japanese Patent Application Laid-Open No. 56-71,074
(4) Japanese Patent Application Laid-Open No. 57-98,270
(5) Japanese Patent Application Laid-Open No. 58-157,768
(6) Japanese Patent Application Laid-Open No. 62-240,683
(7) Japanese Patent Application Laid-Open No. 63-23,868
(8) Japanese Patent Application Laid-Open No. 1-287,071
(9) European Patent Laid-Open No. 324,377
(10) U.S. Patent No. 4,880,804
(11) U.S. Patent No. 4,916,129
(12) Japanese Patent Application No. 2-138,653

Among the compounds disclosed in the patents supra or described in the publications supra, a group of preferred compounds and preferred examples are shown below.

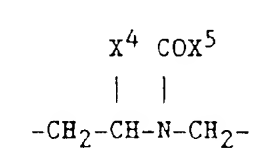
A group of compounds preferred as the non-peptide type compounds having an angiotensin II receptor-antagonizing activity which are the effective ingredient of the composition for the prevention or treatment of hyperuricemia are represented by general formula (I) below.



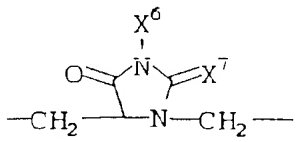
(I)

(wherein each of Z^1, Z^2, and Z^3, independently represents:
nitrogen atom,
a group represented by general formula: $=C(X^2)-$ or,
a group represented by general formula: $=C(X^3)-$; each of X^1, X^2, and X^3 independently represents:
hydrogen,
hydroxy,
mercapto,
halogen,
formyl,
carboxyl,
carbamoyl,
methoxycarbonyl,
ethoxycarbonyl,
an alkyl group having 1 to 10 carbon atoms (wherein the alkyl group may be substituted with a substituent selected from the group consisting of hydroxy, methoxy, ethoxy, halogen, carboxyl, methoxycarbonyl, ethoxycarbonyl, methoxycarbonylamino, cyano, carbamoyl, acetoxy, acetamido, mercapto, methylthio, ethylthio, phenyl and tetrazolyl,
an alkyl group having 2 to 5 carbon atoms (wherein the alkenyl group may be substituted with a substituent selected from the group consisting of hydroxy, methoxy, ethoxy, carboxyl, methoxycarbonyl and ethoxycarbonyl, alkynyl having 2 to 5 carbon atoms, cycloalkyl having 3 to 6 carbon atoms, alkoxy having 1 to 4 carbon atoms, alkylthio having 1 to 4 carbon atoms, thienyl, or phenyl (wherein the phenyl may be substituted with 1 to 3 substituents selected from the group consisting of hydroxy, halogen, methoxy, ethoxy, n-propoxy, n-butoxy, mercapto, methylthio, ethylthio, n-propylthio, n-butylthio, methyl, ethyl, n-propyl, isopropyl, n-butyl, nitro, amino, methylamino, dimethylamino, ethylamino, diethylamino, n-propylamino, n-butylamino, phenyl,

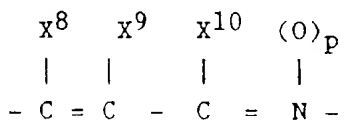
phenoxy, benzyl, benzyloxy, carboxyl, methoxycarbonyl, ethoxycarbonyl and carbamoyl;
when Z^2 and Z^3 represent a group of general formula:
$=C(X^2)-$ or a group of general formula: $=C(X^3)-$, X^2 and X^3 may be combined together to form:
a group represented by general formula:



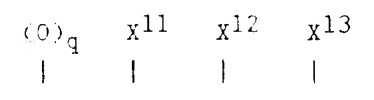
(wherein X^4 represents carboxyl, carbamoyl, formyl, cyano or hydroxymethyl, and X^5 represents fluorenyl, phenyl(methyl)amino, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclohexyl-(phenyl-)methyl or benzhydryl:
(wherein the phenyl in benzhydryl may be substituted with a substituent selected from the group consisting of halogen, hydroxy, methoxy, ethoxy, mercapto, methylthio, ethylthio, amino, methylamino, dimethylamino, ethylamino, diethylamino, methyl and ethyl));
a group represented by general formula:



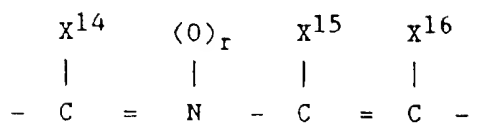
(wherein X^6 represents alkyl having 1 to 4 carbon atoms or phenyl:
(wherein the phenyl may be substituted with 1 or 2 substituents selected from the group consisting of halogen, methyl, ethyl, hydroxy, methoxy, ethoxy, mercapto, methylthio, ethylthio, amino, methylamino, dimethylamino, ethylamino and diethylamino; and X^7 represents an oxygen atom or sulfur atom);
a group represented by general formula:



(wherein each of X^8, X^9 and X^{10} independently represents hydrogen, alkyl of 1 to 6 carbon atoms): (wherein the alkyl group may be substituted with hydroxy, amino, mercapto, methoxy, methylthio, carboxyl, carbamoyl, acetylamino or acetoxy); alkoxycarbonyl group having 2 to 5 carbon atoms, halogen, cyano, carboxyl, carbamoyl, acetyl, amino, mono- or dialkylamino having 1 to 6 carbon atoms which may be substituted with an amino, pyrrolidinyl, piperidino, piperazino, morpholino, thiomorpholino, triazolyl, tetrazolyl, trichloromethyl, tribromomethyl, trifluoromethyl or phenyl (wherein the phenyl may be substituted with methyl, ethyl, methoxy, ethoxy, hydroxy, methylthio, ethylthio, mercapto, carboxyl and cyano); and p represents 0 or 1);
a group represented by general formula:

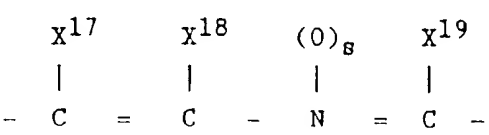


(wherein each of X^{11}, X^{12}, and X^{13} independently has the same significance as X^8, X^9 or X^{10}, and q has the same significance as p);
a group represented by general formula:



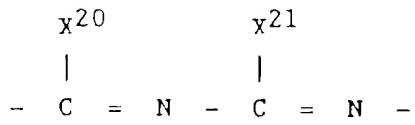
(wherein each of X^{14}, X^{15} and X^{16} independently has the same significance as X^8, X^9 of X^{10}, and r has the same significance as p);

a group represented by general formula:



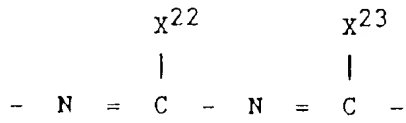
(wherein each of X^{17}, X^{18} and X^{19} independently has the same significance as X^8, X^9 or X^{10}, and s has the same significance as p);

a group represented by general formula:



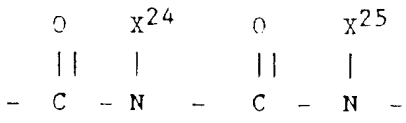
(wherein each of X^{20} and X^{21} independently has the same significance as X^8, X^9 or X^{10});

a group represented by general formula:



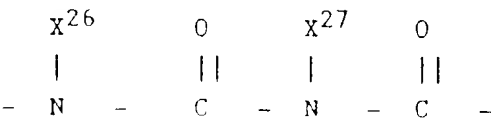
(wherein each of X^{22} and X^{23} independently has the same significance as X^8, X^9 or X^{10});

a group represented by general formula:

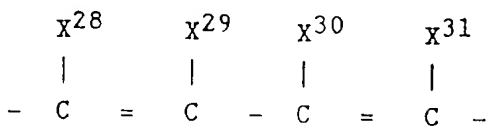


(wherein each of X^{24} and X^{25} independently represents hydrogen or alkyl of 1 to 4 carbon atoms (wherein the alkyl group may be substituted with a substituent selected from the group consisting of hydroxy, methoxy, ethoxy, methoxycarbonyl, carboxyl, ethoxycarbonyl and carbamoyl));

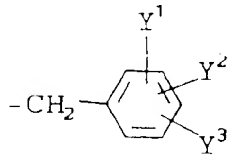
a group represented by general formula:



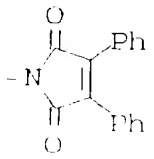
(wherein each of X^{26} and X^{27} independently has the same significance as X^{24} and X^{25}); or,
a group represented by general formula:



(wherein each of X^{28}, X^{29}, X^{30} and X^{31} independently represents hydrogen, an alkyl group having 1 to 4 carbon atoms (wherein the alkyl group may be substituted with a substituent selected from the group consisting of hydroxy, methoxy, ethoxy, carboxyl, methoxycarbonyl, ethoxycarbonyl, carbamoyl, acetyl, acetoxy, acetamido and halogen), halogen, a perfluoroalkyl group having 1 to 6 carbon atoms, carboxyl, carbamoyl, cyano, formyl, methoxy, ethoxy, propoxy, methoxycarbonyl or ethoxycarbonyl);
Y represents:
phenethyl,
cyclohexylethyl,
adamantylethyl,
or a group represented by general formula:

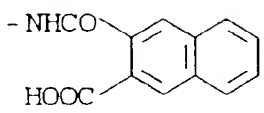


(wherein each of Y^1 and Y^2 independently represents:
hydrogen,
halogen,
nitro,
carboxyl,
amino,
cyano,
formyl,
hydroxyiminomethyl,
trifluoromethylsulfonylamino,
trifluoroacetylamino,
an alkoxy group having 1 to 4 carbon atoms,
an alkyl group having 1 to 4 carbon atoms,
carboxymethyl, tetrazolylmethyl,
a group represented by formula:

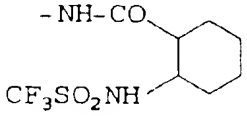


a group represented by general formula:
$-NHCO(CH_2)_tCOOH$
(wherein t represents 1 to 3):
a group represented by formula: $-NHCOCH=CH-CO_2H$,
a group represented by formula:

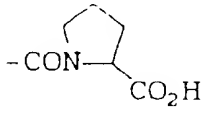
-NHCOCH$_2$CH(Ph)CO$_2$H;
a group represented by formula:
-NHCOCH(Ph)CH$_2$CO$_2$H;
a group represented by formula



a group represented by formula:

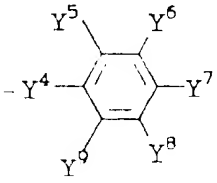


a group represented by formula: -CONHCH(Ph)CO$_2$H;
a group represented by formula:



a group represented by formula:
-NHCOC(Ph)=C(Ph)CO$_2$H;
phthalimido;
benzyloxy;
a mono- or dialkylamino having 1 to 4 carbon atoms;
acetoxy; or,
propionyloxy;

Y^3 represents:
hydrogen; or,
a group represented by general formula:



(wherein Y^4 represents a single bond; oxygen; sulfur; carbonyl;
a group of formula: -NH-,
a group of formula: -CH=CH-
a group of general formula: -N(Y^{10})CO- (wherein Y^{10} represents hydrogen, methyl or phenyl);
a group of general formula: -CON(Y^{11})- (wherein Y^{11} represents hydrogen, methyl or phenyl);
a group of formula: -CH$_2$HH-;
a group of formula: -NHCH$_2$-;
a group of general formula: -CH$_2$-Y^{12}- (wherein Y^{12} represents oxygen or sulfur);
a group of general formula -Y^{13}-CH$_2$- (wherein Y^{13} represents oxygen or sulfur); or

a group of formula: -NHCONH-;

each of Y^5, Y^6, Y^7, Y^8 and Y^9 independently represents an alkyl group having 1 to 4 carbon atoms, halogen, carboxyl, carbamoyl, hydroxy, methoxy, ethoxy, mercapto, methylthio, ethylthio, sulfo, sulfamoyl, nitro, trifluoromethanesulfonylamino, methanesulfonylamino, benzenesulfonylamino, 4-chlorobenzenesulfonylamino, acetylaminosulfonylmethyl, methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl, amino, formyl, phospho, phosphono or cyano).

Herein, terms used in the description on the group of preferred compounds are specifically explained.

The halogen atom refers to fluorine atom, chlorine atom, bromine atom or iodine atom.

The alkyl group having 1 to 10 carbon atoms refers to a straight or branched alkyl group having 1 to 10 carbon atoms, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, n-hexyl, isohexyl, n-heptyl, n-octyl, n-nonyl, n-decanyl or the like.

The alkenyl group having 2 to 5 carbon atoms refers to straight or branched alkenyl group having 2 to 5 carbon atoms, for example, vinyl, 1-methylvinyl, 1-propenyl, 2-methylpropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-1-butenyl, 3-methyl-2-pentenyl, or the like.

The alkynyl group having 2 to 5 carbon atoms refers to a straight or branched alkynyl group having 2 to 5 carbon atoms, for example, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 3-methyl-1-propynyl, 3-methylbutynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, or the like.

The alkoxy group having 1 to 4 carbon atoms refers to an alkoxy group, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, or the like.

The alkylthio group having 1 to 4 carbon atoms refers to an alkylthio group, for example, methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, isobutylthio, tert-butylthio, or the like.

The alkyl group having 1 to 6 carbon atoms refers to a straight or branched alkyl group having 1 to 6 carbon atoms, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, n-hexyl or the like.

The mono- or dialkylamino group having 1 to 6 carbon atoms refers to a mono- or dialkylamino group, for example, methylamino, ethylamino, n-propylamino, n-butylamino, isobutylamino, n-pentylamino, n-hexylamino, dimethylamino, diethylamino, dipropylamino, or the like.

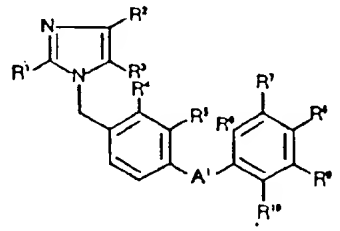
The perfluoroalkyl group having 1 to 6 carbon atoms refers to an alkyl group wherein hydrogen atoms in a straight or branched alkyl group having 1 to 6 carbon atoms are all substituted with fluorine atoms and is shown by, for example, formulae: CF_3, CF_2CF_3, $CF_2CF_2CF_3$, $CF(CF_3)2$, $CF_2CF_2CF_2CF_3'$, $CF_2CF(CF_3)_2$, $CF_2CF_2CF_2CF_2CF_2CF_3$, $CF_2CF_2CF_2CF_2CF_3$ or $CF_2CF_2CF(CF_3)_2$, or the like.

The alkyl group having 1 to 4 carbon atoms refers to a straight or branched alkyl group having 1 to 4 carbon atoms, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, or the like.

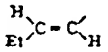
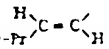
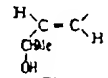
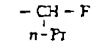
The alkoxycarbonyl group having 2 to 5 carbon atoms refers to an alkyl ester having 2 to 5 carbon atoms, for example, methoxycarbonyl group, ethoxycarbonyl group, n-propoxycarbonyl group, isopropoxycarbonyl group, n-butoxycarbonyl group, isobutoxycarbonyl group, tert-butoxycarbonyl group, or the like.

As the pharmaceutically acceptable non-toxic salts of the non-peptide type compounds for the prevention or treatment of hyperuricemia having an angiotensin II receptor-antagonizing activity, any salts may be used as long as they are acceptable as drugs. Examples of the salts include salts with inorganic or organic bases such as ammonium salt, sodium salt, potassium salt, magnesium salt, triethylamine salt, dicyclohexylamine salt, N-methylglucamine salt, or the like; salts with amino acids such as arginine, lysine, or the like; salts with inorganic or organic acids such as hydrochloride, hydrobromide, sulfate, phophate, methanesulfonate, toluenesulfonate, maleate, fumarate, camphorsulfonate, or the like.

Next, preferred examples of the non-peptide type compounds having an angiotensin II receptor-antagonizing activity in accordance with the present invention are shown in Tables 1 through 10.



No.	R¹	R²	R³	R⁴	R⁵	A¹	R⁶	R⁷	R⁸	R⁹	R¹⁰
1	n-Bu	Cl	CH_2CO_2Me	H	H	-NHCO-	CO_2Na	H	H	H	H
2	"	"	$(CH_2)_2CO_2Me$	"	"	"	CO_2H	"	"	"	"
3	"	"	CH_2CO_2Me	"	"	"	$-NSO_2CF_3$ Na	"	"	"	"
4	"	"	CH_2CO_2H	"	"	single bond	CO_2H	"	"	"	"
5	"	"	CO_2H	"	"	"	"	"	"	"	"
6	"	"	CHO	"	"	"	"	"	"	"	"
7	Et-CH = CH	"	CH_2OH	"	"	"	"	"	"	"	"
8	"	"	CHO	"	"	"	"	"	"	"	"
9	n-Bu	"	CH_2OH	"	"	"	Tet · K	"	"	"	"
10	"	"	"	"	"	"	CO_2H	"	"	"	"
11	"	"	$(CH_2)_2CO_2H$	"	"	"	H	"	"	"	"
12	"	"	CH_2OH	"	"	"	"	"	CO_2H	"	"
13	"	"	CH_2OMe	"	"	"	"	CO_2H	H	"	"
14	"	"	CH_2OH	"	"	"	CO_2H	H	"	"	"
15	"	"	"	"	"	"	$CONH_2$	"	"	"	"
16	"	"	$(CH_2)_2$-Tet	"	"	"	H	"	"	"	"
17	"	"	CH_2CO_2Na	"	"	-NHCO-	CO_2Na	"	"	"	"
18	"	"	CH_2CO_2Me	"	"	"	"	"	"	"	"
19		"	CH_2OH	"	"	single bond	CO_2H	"	"	"	"
20	n-Bu	"	"	"	"	$-OCH_2-$	"	"	"	"	"

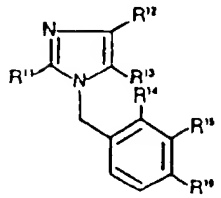
No.	R²	R³	R⁴	R⁵	R⁶	A¹	R⁷	R⁸	R⁹	R¹⁰	R¹¹
21	n-Bu	Cl	CH_2OH	H	H	-O-	CO_2H	H	H	H	H
22	〃	〃	〃	〃	〃	-S-	〃	〃	〃	〃	〃
23	〃	〃	〃	〃	〃	-NH-	〃	〃	〃	〃	〃
24	〃	〃	〃	〃	〃	-CO-	〃	〃	〃	〃	〃
25	〃	〃	〃	〃	〃	single bond	〃	〃	〃	〃	〃
26		〃	〃	〃	〃	〃	〃	〃	〃	〃	〃
27	n-Pr	〃	〃	〃	〃	〃	〃	〃	〃	〃	〃
28	n-Bu	〃	〃	〃	〃	〃	〃	〃	〃	〃	〃
29	n-Pen	〃	〃	〃	〃	〃	〃	〃	〃	〃	〃
30	Et	〃	〃	〃	〃	〃	〃	〃	〃	〃	〃
31		〃	〃	〃	〃	〃	〃	〃	〃	〃	〃
32	n-Bu-S-	〃	〃	〃	〃	〃	〃	〃	〃	〃	〃
33		〃	〃	〃	〃	〃	〃	〃	〃	〃	〃
34	Ph	〃	〃	〃	〃	〃	〃	〃	〃	〃	〃
35	CH_2OH	〃	〃	〃	〃	〃	〃	〃	〃	〃	〃
36		〃	〃	〃	〃	〃	〃	〃	〃	〃	〃
37	n-Bu	〃	〃	〃	〃		〃	〃	〃	〃	〃
38	〃	〃	〃	〃	〃	-NHCONH-	〃	〃	〃	〃	〃
39	〃	〃	〃	〃	〃	single bond	Tet	〃	〃	〃	〃
40	〃	〃	CH_2CO_2Me	〃	〃	-NHCO-	Me	〃	〃	〃	〃
41	〃	〃	〃	〃	〃	$-NHCH_2-$	H	〃	〃	〃	〃
42	〃	〃	〃	〃	〃	-NHCO-	CO_2H	〃	〃	〃	〃
43	〃	CH_2COOMe	Cl	〃	〃	〃	〃	〃	〃	〃	〃
44	〃	Cl	CH_2OMe	〃	〃	〃	〃	〃	〃	〃	〃
45	〃	〃	CH_2CO_2Me	〃	〃	〃	〃	F	F	F	F
46	〃	〃	〃	〃	〃	〃	〃	H	H	Me	H

No.	R¹	R²	R³	R⁴	R⁵	A¹	R⁶	R⁷	R⁸	R⁹	R¹⁰
47	n-Bu	Cl	CH_2CO_2Me	H	H	-NHCO-	CO_2H	H	Me	H	H
48	〃	〃	〃	〃	〃	〃	〃	〃	H	NO_2	〃
49	〃	〃	〃	〃	〃	〃	〃	〃	NO_2	H	〃
50	〃	〃	〃	〃	〃	〃	〃	〃	H	〃	NO_2
51	〃	〃	〃	〃	〃	〃	〃	〃	〃	〃	OMe
52	〃	〃	〃	〃	〃	〃	〃	〃	〃	〃	Me
53	〃	〃	〃	〃	〃	〃	〃	Cl	〃	〃	Cl
54	〃	〃	CH_2OMe	〃	〃	〃	〃	〃	〃	〃	〃
55	〃	〃	〃	〃	〃	-NCO- | Me	〃	〃	〃	〃	〃
56	〃	〃	CH_2CO_2Me	〃	〃	-NHCO-	O-CP	H	〃	〃	H
57	〃	〃	〃	〃	〃	〃	$CF_3SO_2\overset{H}{N}$	〃	〃	〃	〃
58	〃	〃	〃	〃	〃	-NCO- | Ph	〃	〃	〃	〃	〃
59	〃	〃	〃	〃	〃	-NHCO-	$MeSO_2\overset{H}{N}$	〃	〃	〃	〃
60	〃	〃	〃	〃	〃	〃	$CF_3SO_2\overset{H}{N}$	〃	〃	Cl	〃
61	〃	〃	〃	〃	〃	〃	〃	〃	〃	Br	〃
62	〃	〃	〃	〃	〃	〃	〃	〃	〃	I	〃
63	〃	〃	〃	〃	〃	〃	〃	〃	〃	Me	〃
64	〃	〃	〃	〃	〃	〃	〃	Me	〃	H	〃
65	〃	〃	〃	〃	〃	〃	H	H	NO_2	〃	〃
66	〃	〃	〃	〃	〃	〃	〃	〃	Cl	〃	〃
67	〃	〃	〃	〃	〃	〃	HO	NO_2	H	NO_2	〃
68	〃	〃	CH_2OMe	〃	〃	〃	HO_3S	H	〃	H	〃
69	〃	〃	CH_2CO_2Me	〃	〃	〃	H	$CF_3SO_2\overset{H}{N}$	〃	〃	〃
70	〃	〃	〃	〃	〃	〃	〃	H	$CF_3SO_2\overset{H}{N}$	〃	〃
71	H	H	H	〃	〃	〃	CO_2H	〃	H	〃	〃
72	Me	〃	〃	〃	〃	〃	〃	〃	〃	〃	〃

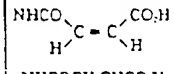
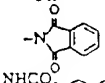
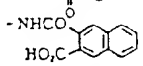
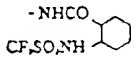
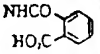
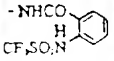
No.	R¹	R²	R³	R⁴	R⁵	A¹	R⁶	R⁷	R⁸	R⁹	R¹⁰
73	Et	H	H	H	H	-NHCO-	CO_2H	H	H	H	H
74	n-Pr	〃	〃	〃	〃	〃	〃	〃	〃	〃	〃
75	n-Bu	〃	〃	〃	〃	〃	〃	〃	〃	〃	〃
76	n-Pen	〃	〃	〃	〃	〃	〃	〃	〃	〃	〃
77	n-Hex	〃	〃	〃	〃	〃	〃	〃	〃	〃	〃
78	n-Hep	〃	〃	〃	〃	〃	〃	〃	〃	〃	〃
79	$Ph(CH_2)_3$	〃	〃	〃	〃	〃	〃	〃	〃	〃	〃
80	p-MP	〃	〃	〃	〃	〃	〃	〃	〃	〃	〃
81	c-Hex	〃	〃	〃	〃	〃	〃	〃	〃	〃	〃
82	i-Pr	H	H	〃	〃	〃	〃	〃	〃	〃	〃
83	$Ph(CH_2)_3$	Cl	CH_2OH	〃	〃	〃	〃	〃	〃	〃	〃
84	H	H	〃	〃	〃	〃	〃	〃	〃	〃	〃
85	n-Bu	Cl	OMe	〃	〃	-CONH-	〃	〃	〃	〃	〃
86	〃	〃	〃	〃	〃	〃	〃	Me	〃	〃	〃
87	〃	〃	〃	〃	〃	〃	Tet	H	〃	〃	〃
88	〃	〃	CH_2CO_2Me	〃	〃	-NHCO-	CO_2H	〃	〃	〃	〃
89	〃	〃	CH_2OH	〃	〃	single bond	H	CO_2Me	〃	〃	〃
90	〃	〃	〃	〃	〃	〃	〃	CO_2H	〃	〃	〃
91	〃	〃	〃	〃	〃	$-OCH_2-$	〃	H	〃	〃	〃
92	〃	〃	〃	〃	〃	〃	CO_2H	〃	〃	〃	〃
93	n-Pr-S	H	CO_2Et	〃	〃	〃	H	〃	〃	〃	〃
94	〃	〃	CH_2OH	〃	〃	〃	〃	〃	〃	〃	〃
95	〃	〃	〃	〃	〃	〃	CO_2H	〃	〃	〃	〃
96	n-Bu	Cl	〃	〃	〃	-CO-	CO_2Me	〃	〃	〃	〃
97	〃	〃	CH_2OMe	〃	〃	〃	CO_2H	〃	〃	〃	〃
98	〃	〃	CH_2OH	〃	〃		CN	〃	〃	〃	〃

No.	R¹	R²	R³	R⁴	R⁵	A¹	R⁶	R⁷	R⁸	R⁹	R¹⁰
99	n-Bu	Cl	CH_2OH	H	H		CO_2H	H	H	H	H
100	〃	〃	CH_2OMe	〃	〃	-NHCONH-	NO_2	〃	〃	〃	〃
101	〃	〃	〃	〃	〃	〃	NH_2	〃	〃	〃	〃
102	〃	〃	〃	〃	〃	〃		〃	〃	〃	〃
103	〃	〃	CH_2CO_2Me	〃	〃	-NHCO-	CO_2H	〃	〃	〃	〃
104	〃	〃	CH_2OH	〃	〃	single bond	H	CO_2H	〃	〃	〃
105	〃	H	〃	〃	〃	〃	〃	〃	〃	〃	〃
106	〃	Cl	CH_2CO_2Me	〃	〃	〃	〃	〃	〃	〃	〃
107	〃	〃	CH_2OMe	〃	〃	〃	〃	〃	〃	〃	〃
108	〃	〃	CH_2OH	〃	〃	-CO-	CO_2H	〃	〃	〃	〃
109	〃	CH_2OH	Cl	〃	〃	〃	〃	〃	〃	〃	〃
110	〃	CH_2OCOMe	〃	〃	〃	〃	〃	〃	〃	〃	〃
111	〃	Cl	CH_2NHCO_2Me	〃	〃	〃	〃	〃	〃	〃	〃
112	〃	〃	CH_2OMe	〃	〃	〃	〃	〃	〃	〃	〃
113	〃	〃	CH_2OH	〃	〃	-O-	〃	〃	〃	〃	〃
114	〃	〃	〃	〃	〃	-S-	〃	〃	〃	〃	〃
115	〃	H	〃	〃	〃	$-OCH_2-$	〃	〃	〃	〃	〃
116	〃	Cl	CH_2OCOMe	〃	〃	〃	〃	〃	〃	〃	〃
117	〃	〃	CH_2OMe	〃	〃	〃	〃	〃	〃	〃	〃
118	n-Pr-S	H	CH_2OH	〃	〃	〃	〃	〃	〃	〃	〃
119	EtS	〃	〃	〃	〃	〃	〃	〃	〃	〃	〃

TABLE 2



No.	R^{11}	R^{12}	R^{13}	R^{14}	R^{15}	R^{16}
120	n-Bu	Cl	CH_2CO_2Na	Cl	H	H
121	"	"	"	NO_2	"	"
122	"	"	"	H	"	CO_2Na
123	"	"	CH_2CO_2H	NO_2	"	H
124	"	"	CH_2CO_2Na	NO_2	"	"
125	"	"	CH_2CO_2H	H	"	NO_2
126	"	"	CH_2CO_2Me	NO_2	"	H
127	"	"	CH_2CO_2H	H	"	NH_2
128	"	"	CH_2CO_2Na	"	"	CO_2Na
129	"	"	"	"	"	H
130	"	"	"	Me	OMe	"
131	"	"	CH_2CO_2Me	NO_2	H	"
132	"	"	CH_2CO_2H	H	"	"
133	"	"	"	Cl	"	"
134	"	"	"	"	"	CO_2H
135	"	"	CH_2CO_2Me	H	"	NH_2
136	"	"	CH_2OMe	"	"	"
137	"	"	CH_2OH	"	"	"
138	"	CH_2CO_2H	Cl	"	"	CO_2H
139	"	Cl	CH_2OH	"	"	"
140	"	CH_2OH	Cl	"	"	"

No.	R^{11}	R^{12}	R^{13}	R^{14}	R^{15}	R^{16}
141	n-Bu	Cl	CH_2CO_2Me	H	H	CO_2H
142	"	"	CH_2CO_2H	"	"	CH_2CO_2H
143	"	"	CH_2COOMe	"	"	NO_2
144	"	"	CH_2CO_2H	"	"	CHO
145	"	"	"	"	"	CH = NOH
146	"	"	"	"	"	OMe
147	"	"	CH_2COOMe	"	"	
148	"	"	"	"	"	$NHCO(CH_2)_2CO_2H$
149	"	"	"	"	"	$NHCO(CH_2)_3CO_2H$
150	"	"	"	"	"	
151	"	"	CH_2OCH_3	"	"	$NHCOCH_2CHCO_2H$ (Ph)
152	"	"	"	"	"	$NHCOCHCH_2CO_2H$ (Ph)
153	"	"	CH_2CO_2Me	"	"	
154	"	"	"	"	"	
155	"	"	"	"	"	$NHSO_2CF_3$
156	"	"	"	"	"	$NHCOCF_3$
157	"	"	$-CH_2-Tet$	"	"	$-CH_2-Tet$
158	"	"	CH_2CO_2Me	"	"	
159	"	"	CH_2CO_2H	"	CO_2H	H
160	"	"	"	CO_2H	H	"
161	"	"	CH_2-Tet	H	CH_2-Tet	"
162	"	"	CH_2CO_2Me		H	"
163	"	"	"		"	"

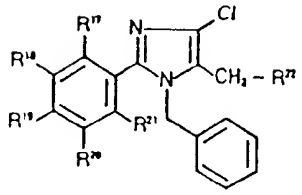
No.	R^{11}	R^{12}	R^{13}	R^{14}	R^{15}	R^{16}
164	n-Bu	Cl	OMe	H	H	CO-L-Phe
165	"	"	"	"	"	CO-D-Phe
166	"	"	"	"	"	CO-L-Pro
167	"	"	"	"	"	-CO-D-Pro
168	"	"	CH_2OH	"	"	NO_2
169	"	"	"	"	NO_2	H
170	"	"	"	NO_2	H	"
171	"	"	"	H	"	CN
172	"	"	"	"	CN	H
173	"	"	"	CN	H	"
174	"	CH_2OH	Cl	H	"	NO_2
175	"	"	"	"	NO_2	H
176	"	"	"	NO_2	H	"
177	"	"	"	H	"	CN
178	"	"	"	"	CN	H
179	"	"	"	CN	H	"
180	"	"	"	H	"	CHO
181	"	"	"	"	"	OMe
182	"	Cl	CH_2CN	"	"	NO_2
183	"	"	"	"	NO_2	H
184	"	"	"	NO_2	H	"
185	"	"	"	H	"	CN
186	"	"	"	"	CN	H

No.	R^{11}	R^{12}	R^{13}	R^{14}	R^{15}	R^{16}
187	*n*-Bu	Cl	CH_2COOH	H	H	NO_2
188	〃	〃	〃	〃	NO_2	H
189	〃	〃	〃	NO_2	H	〃
190	〃	〃	CH_2OMe	H	〃	NO_2
191	〃	〃	CH_2CO_2Me	〃	NO_2	H
192	〃	〃	〃	NH_2	H	〃
193	〃	〃	CH_2OCH_3	H	〃	NHMe
194	〃	〃	CH_2CO_2Me	$-NHCOC(Ph)(Ph)-C(Ph)(Ph)-CO_2H$	〃	H
195	〃	〃	〃	H	$-NHCOC(Ph)(Ph)-C(Ph)(Ph)-CO_2H$	〃
196	〃	〃	〃	〃	H	$-NHCOC(Ph)(Ph)-C(Ph)(Ph)-CO_2H$
197	〃	〃	CH_2OMe	$-NHCOC(Ph)(Ph)-C(Ph)(Ph)-CO_2H$	〃	H
198	〃	〃	〃	H	$-NHCOC(Ph)(Ph)-C(Ph)(Ph)-CO_2H$	〃
199	〃	〃	〃	〃	H	$-NHCOC(Ph)(Ph)-C(Ph)(Ph)-CO_2H$
200	HS	H	CH_2OH	〃	〃	NO_2
201	H	〃	〃	〃	〃	〃
202	*n*-Bu	Cl	CH_2OMe	〃	〃	CO_2Me
203	〃	〃	〃	〃	〃	CO_2H
204	Et	〃	CH_2CO_2H	〃	〃	H
205	*i*-Pr	〃	〃	〃	〃	〃
206	*n*-Bu	〃	〃	〃	〃	〃
207	〃	〃	〃	Cl	〃	〃
208	〃	〃	〃	NO_2	〃	〃
209	*n*-Pr	〃	〃	H	〃	〃

No.	R^{a}	R^{b}	R^{c}	R^{d}	R^{e}	R^{f}
210	*t*-Bu	*Cl*	CH_2CO_2H	H	H	H
211	*n*-Pen	〃	〃	〃	〃	〃
212	〃	〃	〃	Cl	〃	〃
213	*n*-Hex	〃	〃	〃	〃	〃
214	*c*-Pen	〃	〃	H	〃	〃
215	*c*-Hex	〃	〃	〃	〃	〃
216	*n*-Bu	〃	〃	〃	〃	*n*-Bu-O
217	Ph-	〃	〃	*Cl*	〃	H
218	〃	〃	〃	H	〃	*n*-Bu-O
219	*n*-Bu	〃	〃	*Cl*	Me	H
220	〃	〃	〃	H	〃	MeO
221	*n*-Hex	〃	〃	〃	〃	〃
222	Ph	〃	〃	〃	〃	EtO
223	*n*-Bu	〃	〃	〃	〃	MeO
224	*n*-Hex	〃	〃	〃	〃	〃
225	Ph	〃	〃	〃	〃	HO
226	〃	〃	〃	〃	H	〃
227	〃	〃	〃	〃	Me	MeCOO
228	〃	〃	〃	〃	〃	*n*-Bu-O
229	〃	〃	〃	〃	〃	MeO
230	〃	〃	〃	MeO	H	H
231	〃	〃	〃	H	MeO	〃
232	〃	〃	〃	〃	H	MeO
233	〃	〃	〃	〃	〃	EtO

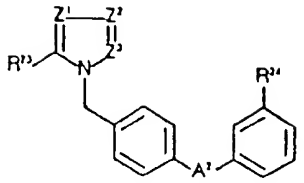
No.	R¹	R²	R³	R⁴	R⁵	R⁶
234	Ph	Cl	CH_2CO_2H	H	H	n-Bu-O
235	〃	〃	〃	〃	〃	$PhCH_2O$
236	〃	〃	〃	〃	MeO	MeO
237	〃	〃	〃	〃	Me	〃
238	Me	〃	〃	〃	H	H
239	n-Bu	〃	CH_2CONH_2	〃	〃	〃
240	〃	CH_2COOH	Cl	Cl	〃	〃
241	Ph	Cl	CH_2CO_2H	H	〃	Me
242	〃	〃	〃	Me	〃	H
243	〃	〃	〃	H	〃	Cl
244	〃	〃	〃	Cl	〃	H
245	〃	〃	〃	〃	〃	Cl
246	〃	〃	〃	Br	〃	〃
247	〃	〃	〃	F	〃	〃
248	〃	Cl	〃	H	〃	〃
249	〃	Br	〃	〃	〃	〃
250		Cl	〃	〃	〃	〃
251	Ph	〃	CH_2CO_2Et	〃	〃	〃
252	〃	〃	CH_2CO_2H	〃	〃	NH_2
253	〃	CH_2CO_2H	Cl	〃	〃	H
254	〃	Cl	CO_2H	〃	〃	〃
255	〃	〃	$(CH_2)_2CO_2H$	〃	〃	〃
256	c-Pen	CH_2CO_2H	Cl	〃	〃	〃
257	Ph	Cl	CH_2CONH_2	〃	〃	〃

TABLE 3



No.	R17	R18	R19	R20	R21	R22
258	H	H	Me	H	H	CO_2H
259	"	"	MeO	"	"	"
260	"	"	n-BuNH	"	"	"
261	NO_2	"	H	"	"	"
262	H	"	NH_2	"	"	"
263	NH_2	"	H	"	"	"
264	H	"	HO	"	"	"
265	"	HO	H	"	"	"
266	HO	H	"	"	"	"
267	H	NO_2	Me_2N	"	"	"
268	"	"	"	NO_2	"	"
269	"	"	Cl	"	"	"
270	"	H	Me_2N	H	"	"
271	"	MeO	H	"	"	"
272	"	H	n-BuO	"	"	"
273	"	"	i-Pr	"	"	"
274	"	"	Me_2N	"	"	$CONH_2$
275	"	Cl	Et_2N	"	"	CO_2H
276	"	"	Me_2N	"	"	"
277	"	Br	"	"	"	"
278	"	HO	HO	"	"	"

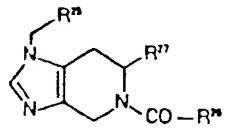
No.	R^1	R^{11}	R^{11}	R^{21}	R^2	R^3
279	H	MeO	H	H	H	CO_2H
280	"	"	HO	"	"	"
281	"	"	MeO	"	"	"
282	"	Me	"	"	"	"
283	"	MeO	$PhCH_2O$	"	"	"



No.	R^{23}	Z^1	Z^2	Z^3	A^2	R^{24}
284	H	C-*n*-Bu	N	N	single bond	CO_2H
285	*n*-Bu	CH	〃	〃	〃	〃
286	〃	〃	〃	〃	〃	Tet
287	H	C-*n*-Bu	〃	〃	〃	〃
288	〃	C-Et	〃	〃	〃	CO_2H
289	Et	CH	〃	〃	〃	〃
290	H	C-*n*-Pr	〃	〃	〃	〃
291	*n*-Pr	〃	〃	〃	〃	〃
292	H	C-*n*-Pen	〃	〃	-CO-	〃
293	*n*-Pen	CH	〃	〃	〃	〃
294	*n*-Bu	N	〃	C-CH_2OMe	single bond	〃
295	〃	〃	〃	CH	〃	〃
296	*n*-Pr	〃	〃	C-CH_2OMe	〃	〃
297	Et	〃	〃	〃	〃	〃
298	*n*-Bu	〃	〃	C-*n*-Bu	〃	〃
299	*n*-Pr	〃	〃	C-CH_2OMe	〃	〃
300	CH_2OMe	CH	C-*n*-Bu	N	〃	〃
301	*n*-Bu	〃	C-CH_2OMe	〃	〃	〃
302	$-(CH_2)_2CH=CH_2$	〃	〃	〃	〃	〃
303	*n*-Pr	〃	〃	〃	〃	〃
304	CH_2OMe	〃	C-*n*-Pr	〃	〃	〃

No.	R^3	Z^1	Z^2	Z^3	A^1	R^4
305	n-Pr	CH	C-COOH	N	single bond	CO_2H
306	"	"	C-CH_2OH	"	"	"
307	CH_2OH	"	C-n-Pr	"	"	"
308	n-Pr	"	C-CHO	"	"	"
309	CHO	"	C-n-Pr	"	"	"
310	n-Pr	"	CH	C-CO_2Et	"	Tet
311	"	"	"	"	"	CO_2H
312	"	"	"	C-CO_2H	"	"
313	"	"	"	C-CHO	"	"
314	n-Bu	"	"	C-CO_2Et	"	Tet
315	"	"	"	C-CO_2H	"	"
316	n-Pr	"	"	C-CHO	"	"

TABLE 5



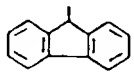
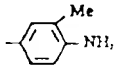
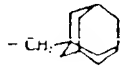
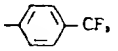
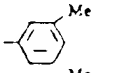
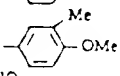
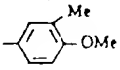
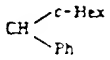
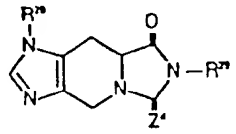
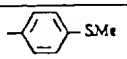
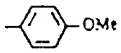
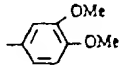
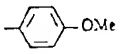
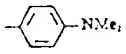
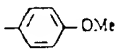
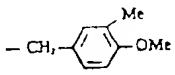
No.	R^m	R^n	R^o
317	Ph	$CHPh_2$	CO_2H
318	"	$CH(-C_6H_4-Cl)_2$	"
319	"		"
320		$CHPh_2$	"
321	Ph		CH_2OH
322		CH_2Ph_2	CO_2H
323		"	"
324	$-CH_2-C-Hex$	"	"
325		"	"
326		"	CH_2OH
327		"	CO_2H
328			"
329	"	$CH_2-c-Hex$	"
330	"	$CHPh_2$	"
331	"	$CH(-C_6H_4-Me)_2$	"
332	CH_2Ph	$CHPh_2$	"
333	Ph	$CH(-C_6H_4-F)_2$	"

TABLE 6



No.	R^{28}	R^{29}	Z^4
334	H		O
335	〃		〃
336	〃		〃
337	〃	i-Pr	〃
338	〃	t-Bu	〃
339	〃	i-Pr	S
340	〃	Pr	〃
341	〃		〃
342	〃		〃
343	CH_2Ph	i-Pr	O
344	〃		S
345	〃	〃	O
346		〃	S
347	〃	〃	O

compound 348

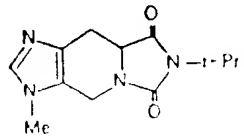
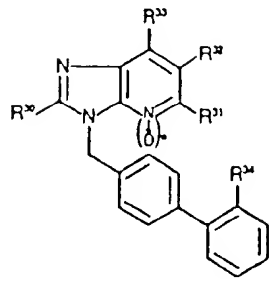


TABLE 7



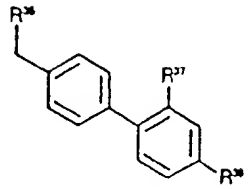
No.	R^{29}	R^{30}	R^{31}	R^{32}	R^{34}	n
349	n-Bu	H	H	H	CO_2H	0
350	"	"	"	"	Tet	"
351	n-Pr	"	"	"	"	"
352	"	"	"	Me	"	"
353	n-Bu	"	"	"	"	"
354	Et	Me	"	"	"	"
355	n-Pr	"	"	"	"	"
356	n-Bu	"	"	"	"	"
357	Et	"	"	"	CO_2H	"
358	n-Pr	NH_2	"	H	Tet	"
359	Et	H	"	Me	"	"
360	Me	"	"	"	"	"
361	n-Pen	"	"	"	"	"
362	n-Non	"	"	"	"	"
363	i-Pr	"	"	"	"	"
364	i-Bu	"	"	"	"	"
365	c-Pr	"	"	"	"	"
366	$MeOCH_2$	"	"	"	"	"
367	n-Pr	"	"	"	CO_2H	"
368	"	"	"	"	$CONHSO_2$	"

No.	R^a	R^b	R^c	R^d	R^e	n
369	n-Pr	H	H	Me	CONHSO$_2$-  -Cl	O
370	"	"	"	"	CONHSO$_2$Me	"
371	c-Pr	Me	"	"	Tet	"
372	"	"	n-Pr	"	"	"
373	n-Pr	H	H	"	CONHSO$_2$CF$_3$	"
374	Et	Me	"	"	NO$_2$	"
375	n-Pr	H	"	"	CH$_3$SO$_2$NHCOMe	"
376	Et	Br	"	"	Tet	"
377	"	Cl	"	"	"	"
378	"	CN	"	"	"	"
379	"	CO$_2$H	"	"	"	"
380	"	CO$_2$Et	"	"	"	"
381	"	CO$_2$Me	"	"	"	"
382	"	CO$_2$CH$_2$Ph	"	"	"	"
383	"	CO$_2$i-Pr	"	"	"	"
384	"	CO$_2$n-Bu	"	"	"	"
385	"	CONH$_2$	"	"	"	"
386	"		"	"	"	"
387	"	i-Pr	"	"	"	"
388	"	Et	"	"	"	"
389	"	n-Hex	"	"	"	"
390	"	Ph	"	"	"	"
391	"	Tet	"	"	"	"
392	"	COMe	"	"	"	"
393	"	MeCHOH-(RS)	"	"	"	"
394	"	CH$_2$OH	"	"	"	"

No.	R[a]	R[x]	R[y]	R[z]	R[w]	n
395	Et	$CH_2CH(OH)Me$	H	Me	Tet	0
396	"	$C(OH)Et_2$	"	"	"	"
397	"	NH_2	"	"	"	"
398	"	"	"	CF_3	"	"
399	"	NHMe	"	Me	"	"
400	"	$NHMe_2$	"	"	"	"
401	n-Pr	"	"	H	"	"
402	Et	NHn-Hex	"	Me	"	"
403	"	$NH(CH_2)_2NH_2$	"	"	"	"
404	"	CH_2CO_2H	"	"	"	"
405	"		"	"	"	"
406	"	SMe	"	"	"	"
407	"	OH	"	"	"	"
408	"	OEt	"	"	"	"
409	"	$(CH_2)_2NHCOMe$	"	"	"	"
410	"	Me	"	H	"	"
411	n-Pr	"	"	"	"	"
412	"	"	Me	"	"	"
413	"	H	Br	Me	"	"
414	"	"	H	Et	"	"
415	"	"	"	i-Pr	"	"
416	Et	"	"	Et	"	"
417	n-Pr	"	CH_2OH	Me	"	"
418	"	"	H		"	"
419	"	"		Me	"	"
420	"	Cl	H	H	"	"

No.	R²	R³	R⁴	R⁵	R⁶	n
421	n-Pr	Me	NH_2	Me	Tet	0
422	"	H	H	"	"	1
423	"	Me	OH	"	"	0
424	CF_3, Me, CH	"	H	"	"	"
425	$HC{\equiv}CH(CH_2)_2$	"	"	"	"	"
426	Me	"	"	"	"	"
427	Et	"	"	Cl	"	"
428	"	"	"		"	"
429	"	"	"	NHMe	"	"
430	"	"	"	NMe_2	"	"
431	"	"	"	SMe	"	"
432	"	CH_2OCOMe	"	Me	"	"

TABLE 8



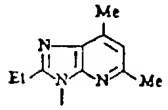
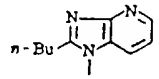
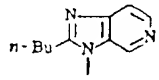
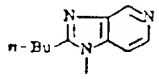
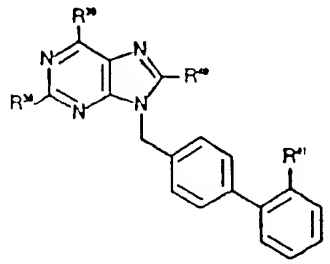
No.	R^{36}	R^{38}	R^{37}
433		Cl	Tet
434	〃	F	〃
435		H	CO_2H
436		〃	〃
437		〃	〃

TABLE 9



No.	R^{39}	R^{38}	R^{40}	R^{41}
438	H	Cl	n-Pr	CO_2H
439	"	"	n-Bu	"
440	"	H	"	"
441	"	Cl	n-Pr	Tet
442	"	H	"	"
443	"	Cl	n-Bu	"
444	"	H	"	"
445	Cl	Me	n-Pr	"
446	Me_2N	"	"	"
447	MeNH	"	"	"
448		"	"	"

compound 449

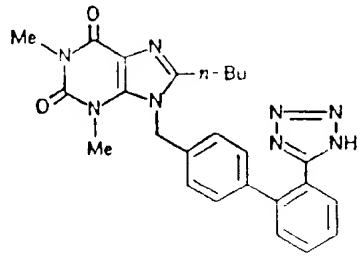
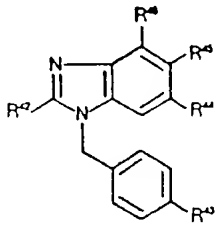
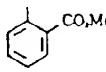
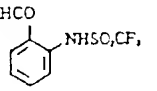
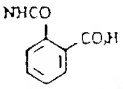
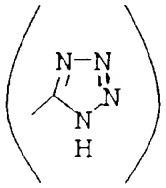


TABLE 10

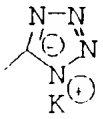


No.	R^{42}	R^{43}	R^{44}	R^{45}	R^{46}
450	n-Bu		OMe	H	H
451	"	"	H	OMe	"
452	"	"	CH_2OH	H	"
453	"	"	H	CH_2OH	"
453	"		"	H	$(CH_2)_3CO_2Et$
454	$CH=CHCO_2Et$	NH_2	"	"	H
455	"	NO_2	"	"	"
456	CH=CH-n-Pr	NH_2	"	"	"
457	"	NO_2	"	"	"
458	CHO	"	"	"	"
459	$(CH_2)_3CO_2Et$	"	"	"	"
460	$(CH_2)_3CO_2H$	"	"	"	"
461	$CH_2CH(CO_2Et)_2$	"	"	"	"
462	"	NH_2	"	"	"
463	CH_2Cl	NO_2	"	"	"
463	CH_2OH	"	"	"	"
464	n-Bu		"	Cl	"

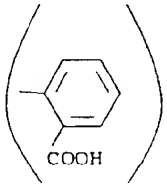
Abbreviations used in this specification and claims are given below.
Tet: tetrazol-5-yl



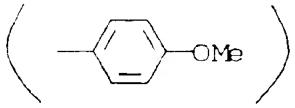
Tet.K: a group shown by formula:



o-CP: 2-carboxyphenyl:



p-MP: 4-methoxyphenyl



Ph: phenyl
Me: methyl
Et: ethyl
n-Pr: n-propyl
i-Pr: isopropyl
c-Pr: cyclopropyl
n-Bu: n-butyl
i-Bu: isobutyl
t-Bu: tert-butyl
n-Pen: n-pentyl
c-Pen: cyclopentyl
n-Hex: n-hexyl
c-Hex: cyclohexyl
n-Non: n-nonyl
L-Pro or D-Pro: L-prolyl or D-prolyl
L-Phe or D-Phe: L-phenylalanyl or D-phenylalanyl

The symbol " at each column means the same as the description at the column right above.

The non-peptide type antiotensin II receptor antagonist itself which is used in the present invention can be prepared and obtained by any one of the processes described in publications (a) through (o) and the patents (1) through (12) supra.

Next, the present invention is described more specifically, with reference to test examples. Test Example: Uric acid excretion activity.

Twenty-four (24) male adults (25 to 48 years old, 161 cm to 187 cm tall, weighing 48 kg to 85 kg) were divided into 4 groups, 6 per group. Compound No. 9 was orally administered under hunger in the form of capsules in Example 2, in a definite dose (25 mg, 50 mg, 100 mg or 200 mg) per person, by varying the dose in each group. Further in order to examine influence of diet on uric acid excretion increasing activity of Compound No. 9, the capsule of Example 2 containing 100 mg of Compound No. 9 was orally administered at 2 weeks after the test under hunger was completed. Concentration of uric acid in urine and blood was determined by the uricase-POD method at every definite period of time after the administration. The results are shown in Tables 11 through 14.

As is clear from Tables 11 through 14, the concentration of uric acid in serum decreased in 4 hours after medication dose-dependently. However, a tendency that the uric acid concentration was recovered to the concentration level prior to medication was noted 24 hours after. On the other hand, when medicated after meals, the concentration of uric acid in serum was kept as it decreased even 24 hours after.

The uric acid concentration in urine dose-dependently increased from 0 to 4 hours by administering Compound no. 9 in doses of 25 mg, 50 mg and 100 mg per person. In the dose of 200 mg, however, the uric acid concentration in urine did not increase dose-dependently but was kept almost constant. On the other hand, when medicated after meals, the uric acid concentration in urine increased in 0 to 8 hours.

The foregoing results reveal that the non-peptide type compounds having an angiotensin II receptor-antagonizing activity in accordance with the present invention have the activities of reducing the uric acid concentration in blood and increasing excretion of uric acid into urine. Accordingly, the non-peptide type compounds having an angiotensin II receptor-antagonizing activity in accordance with the present invention are useful as drugs for the prevention or treatment of hyperuricemia.

Table 11. Change of uric acid concentration in serum with passage of time when administered in hunger

Dose (mg/man) / Time (hr)	Concentration of Uric Acid (mg/dl)			
	25	50	100	200
0 (when administered)	5.2 ± 0.5	6.1 ± 1.4	5.9 ± 0.9	5.6 ± 0.7
4	4.8 ± 0.6	5.3 ± 1.3	4.6 ± 0.7	4.3 ± 0.9
24	4.6 ± 0.6	5.6 ± 1.4	5.2 ± 0.8	5.0 ± 0.9

Table 12. Change in uric acid concentration in serum with passage of time after meal

Time(hr) \ Dose (mg/man)	Concentrarion of Uric Acid (mg/hr)
	100
0 (when administered)	5.8 ± 1.1
4	4.9 ± 1.0
24	4.7 ± 0.9

Table 13. Change in uric acid excretion in urine with passage of time when administered in hunger

Time(hr) \ Dose (mg/man)	Concentration of Uric Acid (mg/hr)			
	25	50	100	200
0 – 4	43.0 ± 24.5	52.8 ± 4.3	81.2 ± 15.7	78.7 ± 15.3
4 – 8	32.4 ± 14.7	42.9 ± 8.5	36.4 ± 7.7	25.4 ± 6.6
8 – 12	28.7 ± 13.6	39.1 ± 4.4	30.1 ± 6.8	19.6 ± 5.2
12 – 24	19.7 ± 9.9	22.2 ± 3.8	19.2 ± 4.2	13.4 ± 2.3
24 – 30	33.2 ± 21.9	26.6 ± 5.4	28.0 ± 7.2	21.0 ± 3.0

Table 14. Change of uric acid excretion in urine with passage of time after meal

Time(hr) \ Dose (mg/man)	Concentration of Uric Acid (mg/hr)
	100
0 - 4	75.9 ± 19.0
4 - 8	59.0 ± 3.8
8 - 12	31.8 ± 4.5
12 - 24	18.9 ± 2.5
24 - 30	29.5 ± 4.1

Where the non-peptide type compounds having an angiotensin II receptor-antagonizing activity in accordance with the present invention are used as compositions for the prevention or treatment of hyperuricemia, the non-peptide type compounds having an angiotensin II receptor-antagonizing activity may be used singly or in the form of pharmaceutical compositions comprising the antagonists and pharmaceutically acceptable carriers.

For preparing the pharmaceutical compositions from the compounds of the present invention, inert and pharmaceutically acceptable carriers may be solid or liquid. The composition in the solid form include powders, tablets, dispersible granules, capsules, cachets and suppositories. The solid carrier may be one or more substances which can also act as a diluent, a flavor, a solubilizing agent, a lubricant, a suspending agent, a binder or a tablet disintegrator. The solid carrier may also be an encapsulated substance. In powder, the carrier is a finely divided solid which is mixed with the active compound. In a tablet, the active compound is mixed with a carrier having a required binding property in an appropriate proportion and the resulting mixture is compressed into a desired shape and size. The powder and tablet contain preferably 5 or 10 to about 70% of the active compound. Suitable examples of the solid carrier include magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, colloidal silicon dioxide, tragacanth gum, sodium carboxymethylstarch, methylcellulose, fine crystalline cellulose, sodium carboxymethylcellulose, low melting point wax, cacao butter, etc. The term preparing into pharmaceutical preparations is contemplated to mean a formulation of an encapsulating substance as a carrier in which the active compound (using or without using any other carrier) is surrounded by the carrier and as the result, the carrier gives a capsule together with the active compound, and the inactive compound. Likewise, a cachet also falls under the term. The tablet, powder, cachet and capsule may be used as a solid form of application suited for oral administration.

In preparing a suppository, a low melting point wax such as a mixture of fatty acid glycerides or cacaco butter is first allowed to melt and the active compound is uniformly dispersed in the melt by, e.g., stirring. The melted homogeneous mixture is then poured into a mold of suitable size, cooled and solidified.

The preparation of liquid form includes a solution, a suspension and an emulsion. Examples of the liquid carier are water for parenteral injection or an aqueous propylene glycol solution. The liquid preparation may also be a solution in a polyethylene glycol aqueous solution The aqueous solution suited for oral application may be prepared by dissolving the active compound in water and, if necessary, adding a suitable coloring agent, a flavor, a stabilizer and a thickener. The aqueous suspension suitable for oral application may be prepared by dispersing the active compound finely divided in water together with a viscous substance, e.g., natural or synthetic rubber, resin, methylcellulose, sodium carboxymethylcellulose and other known suspending agents.

The composition also includes a preparation in a solid form contemplated to be converted into a preparation in a liquid form for oral or parenteral administration just before application. Such a liquid form includes a solution, a suspension and an emulsion. More advantageously, these preparations in a particular solid form may be provided in a single dosage form and used to make a single liquid dosage as it stands. Instead, a sufficient dose of solid may also be provided so as to ensure each liquid dosage in applications several times, by changing to liquid form and then measuring a definite volume of the preparation in a liquid form with a syringe, a teaspoon or other container for determining its volume, etc. In case that liquid dosages to be applied several times are thus provided, it is preferred to maintain the unused portion of the liquid dosage at a low temperature (for

example, under cooling). The preparation in a solid form designed to be converted into a liquid form may contain, in addition to the active compound, a flavor, a coloring agent, a stabilizer, a buffer, an artificial and natural sweetener, a dispersing agent, a thickener, a solubilizing agent, etc. The liquid used to prepare the preparation in a liquid form is water, isotonic water, ethanol, glycerine, propylene glycol, etc. and a mixture thereof. The liquid used is generally chosen in association with mode of application. For example, a liquid preparation containing large quantities of ethanol is inappropriate for parenteral application.

It is preferred that the pharmaceutical preparation may be in a single dosage form. In such a form, the preparation may be divided into a single dose containing a suitable dose of the active compound. The mode of application in a single dose may be a packaged form containing a discontinuous amount of the preparation, for example, a packaged tablet, capsule and powders in a vial or an ampule. The mode of application in a single dose may be a capsule, cachet or a tablet per se or may be a suitable number of any of its packaged forms.

An amount of the active compound in the single dosage of the preparation may be varied or controlled in a range of 0.1 to 500 mg, preferably 1 to 100 mg, depending upon specific application and titer of the active compound. If necessary, the composition may also contain other compatible therapeutic agents.

In the aforesaid therapeutic use, a daily dose range used for a patient weighing 70 kg is 0.1 to 150 mg per 1 kg of body weight, preferably 1 to 100 mg per 1 kg of body weight, in the case of oral administration; in the case of parenteral administration, 0.1 to 50 mg, preferably 0.1 to 20 mg, per 1 kg of body weight. However, the dose may be varied depending upon necessity for patient, condition of disease to be treated and compound to be used.

Determination of an adequate dose for a specific circumstance may be within the skill of a prescriber. In general, treatment is initiated with a dose less than the optimum dose of a compound. Then, the dose is gradually increased until the best effect is achieved under the situation. If necessary for the sake of convenience, a daily dose may be divided and portionwise administered.

The present invention is further described by referring to the following examples but is not deemed to be limited to these examples:

EXAMPLES

EXAMPLE 1 Capsule

Component	Content per Capsule
Compound No. 353	50 mg
Lactose	149 mg
Magnesium stearate	1 mg

Compound No. 353 was prepared into powders having particle size of 60. Lactose and magnesium stearate, which had been similarly passed through blotting paper having a particle size of 60, were added to the powders followed by mixing for 10 minutes. The kneaded mixture was filled up in No. 1 dry gelatin capsule.

EXAMPLE 2 Capsule

Component	Content per Capsule
Compound No. 9	50 mg
Fine crystalline cellulose	115 mg
Lactose	75.5 mg
Magnesium stearate	1.50 mg
Sodium carboxymethyl starch	18.0 mg

Compound No. 9 was prepared into powders having particle size of 60. Fine crystalline cellulose, lactose, magnesium stearate and sodium carboxymethyl starch, which had been similarly passed through blotting paper having a particle size of 60, were added to the powders followed by mixing for 10 minutes. The mixture was filled up in No. 1 dry gelatin capsule. Capsules containing 5 mg or 20 mg of Compound 9 were also prepared in a similar manner.

EXAMPLE 3 Capsule

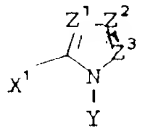
Component	Content per Capsule
Compound No. 9	100 mg
Colloidal silicon dioxide	0.2 mg
Magnesium stearate	5 mg
Fine crystalline cellulose	275 mg
Starch	11 mg
Lactose	98.8 mg

A table was prepared in a conventional manner so as to contain the above components in a dose unit.

Claims

1. A pharmaceutical composition for the prevention or treatment of hyperuricemia comprising a non-peptide type compound or a pharmaceutically acceptable non-toxic salt thereof having an angiotensin II receptor-antagonizing activity.

2. The composition as claimed in claim 1, wherein said non-pedtide type compound having an angiotensin II receptor-antagonizing activity is a compound represented by general formula (I) described below or a pharmaceutically acceptable non-toxic salt thereof:



(I)

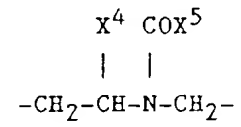
(wherein each of Z^1, Z^2 and Z^3 independently represents:
nitrogen,
a group represented by general formula: $=C(X^2)-$ or,
a group represented by general formula: $=C(X^3)-$; each of X^1, X^2 and X^3 independently represents:
hydrogen,
hydroxy,
mercapto,
halogen,
formyl,
carboxyl,
carbamoyl,
methoxycarbonyl,
ethoxycarbonyl,
an alkyl group having 1 to 10 carbon atoms (wherein said alkyl group may be substituted with a

substituent selected from the group consisting of hydroxy, methoxy, ethoxy, halogen, carboxyl, methoxycarbonyl, ethoxycarbonyl, methoxycarbonylamino, cyano, carbamoyl, acetoxy, acetamido, mercapto, methylthio, ethylthio, phenyl and tetrazolyl),

an alkenyl group having 2 to 5 carbon atoms (wherein said alkenyl group may be substituted with a substituent selected from the group consisting of hydroxy, methoxy, ethoxy, carboxyl, methoxycarbonyl and ethoxycarbonyl), an alkynyl having 2 to 5 carbon atoms, a cycloalkyl group having 3 to 6 carbon atoms, an alkoxy group having 1 to 4 carbon atoms, an alkylthio group having 1 to 4 carbon atoms, thienyl, or phenyl (wherein said phenyl may be substituted with 1 to 3 substituents selected from the group consisting of hydroxy, halogen, methoxy, ethoxy, n-propoxy, n-butoxy, mercapto, methylthio, ethylthio, n-propylthio, n-butylthio, methyl, ethyl, n-propyl, isopropyl, n-butyl, nitro, amino, methylamino, dimethylamino, ethylamino, diethylamino, n-propylamino, n-butylamino, phenyl, phenoxy, benzyl, benzyloxy, carboxyl, methoxycarbonyl, ethoxycarbonyl and carbamoyl);

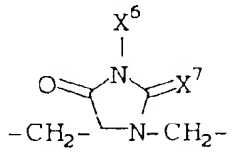
when Z^2 and Z^3 represent a group represented by general formula: $=C(X^2)-$ or a group represented by general formula: $=C(X^3)-$, X^2 and X^3 may be combined together to form:

a group represented by general formula:



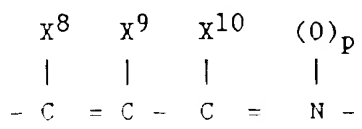
(wherein X^4 represents carboxyl, carbamoyl, formyl, cyano or hydroxymethyl, and, X^5 represents fluorenyl, phenyl(methyl)amino, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclohexyl-(phenyl)methyl or benzhydryl: (wherein phenyl in said benzhydryl group may be substituted with a substituent selected from the group consisting of halogen, hydroxy, methoxy, ethoxy, mercapto, methylthio, ethylthio, amino, methylamino, dimethylamino, ehtylamino, diethylamino, methyl and ethyl));

a group represented by general formula:



(wherein X^6 represents an alkyl group having 1 to 4 carbon atoms or a phenyl:

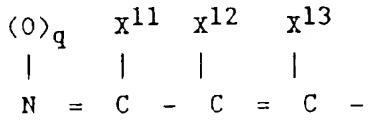
(wherein said phenyl may be substituted with 1 or 2 substituents selected from the group consisting of halogen, methyl, ethyl, hydroxy, methoxy, ethoxy, mercapto, methylthio, ethylthio, amino, methylamino, dimethylamino, ethylamino and diethylamino); and X^7 represents oxygen or sulfur); a group represented by general formula:



(wherein each of X^8, X^9 and X^{10} independently represents hydrogen, or alkyl having 1 to 6 carbon atoms):

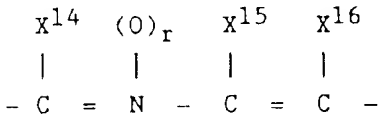
(wherein said alkyl group may be substituted with hydroxy, amino, mercapto, methoxy, methylthio, carboxyl, carbamoyl, acetylamino or acetoxy); an alkoxycarbonyl having 2 to 5 carbon atoms, halogen, cyano, carboxyl, carbamoyl, acetyl, amino, a mono- or dialkylamino group having 1 to 6 carbon atoms which may by substituted with amino, pyrrolidinyl, piperidino, piperazino, morpholino, thiomorpholino, triazolyl, tetrazolyl, trichloromethyl, tribromomethyl, trifluoromethyl or a phenyl (wherein said phenyl may be substituted with a substituent selected from the group consisting of methyl, ethyl, methoxy, ethoxy, hydroxy, methylthio, ethylthio, mercapto, carboxyl, and cyano); and p represents 0 or 1);

a group represented by general formula:



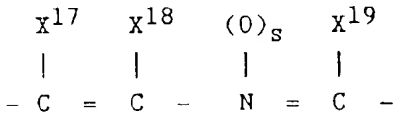
(wherein each of X^{11}, X^{12} and X^{13} independently has the same significance as X^8, X^9 or X^{10}, and q has the same significance as p);

a group represented by general formula:



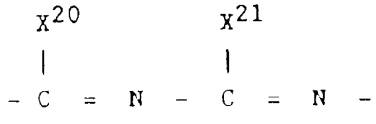
(wherein each of X^{14}, X^{15} and X^{16} independently has the same significance as X^8, X^9 or X^{10}, and r has the same significance as p);

a group represented by general formula:



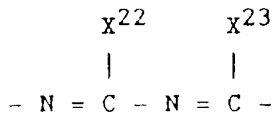
(wherein each of X^{17}, X^{18} and X^{19} independently has the same significance as X^8, X^9 or X^{10}, and s has the same significance as p);

a group represented by general formula:



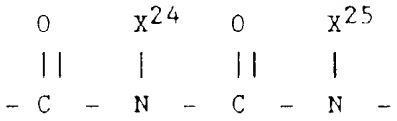
(wherein each of X^{20} and X^{21} independently has the same significance as X^8, X^9 or X^{10});

a group represented by general formula:



(wherein each of X^{22} and X^{23} independently has the same significance as X^8, X^9 or X^{10}),

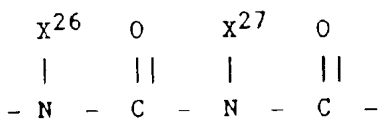
a group represented by general formula:



(wherein each of X^{24} and X^{25} independently represents hydrogen or an alkyl group having 1 to 4

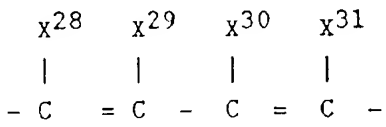
carbon atoms (wherein said alkyl group may be substituted with a substituent selected from the group consisting of hydroxy, methoxy, ethoxy, methoxycarbonyl, carboxyl, ethoxycarbonyl and carbamoyl));

a group represented by general formula:



(wherein each of X^{26} and X^{27} independently has the same significance as X^{24} or X^{25}); or,

a group represented by general formula:



(wherein each of X^{28}, X^{29}, X^{30} and X^{31} independently represents hydrogen, an alkyl group having 1 to 4 carbon atoms (wherein said alkyl group may be substituted with a substituent selected from the group consisting of hydroxy, methoxy, ethoxy, carboxyl, methoxycarbonyl, ethoxycarbonyl, carbamoyl, acetyl, acetoxy, acetylamino and halogen), a halogen, a perfluoroalkyl group having 1 to 6 carbon atoms, carboxyl, carbamoyl, cyano, formyl, methoxy, ethoxy, propoxy, methoxycarbonyl or ethoxycarbonyl);

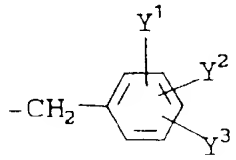
Y represents:

phenethyl,

cyclohexylethyl,

adamantylethyl,

or a group represented by formula:



(wherein each of Y^1 and Y^2 independently represents:

hydrogen,

halogen,

nitro,

carboxyl,

amino,

cyano,

formyl,

hydroxyiminomethyl,

trifluoromethylsulfonylamino,

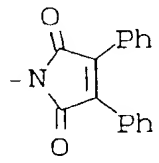
trifluoroacetylamino,

an alkoxy group having 1 to 4 carbon atoms,

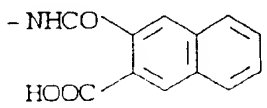
an alkyl group having 1 to 4 carbon atoms,

carboxymethyl, tetrazolylmethyl,

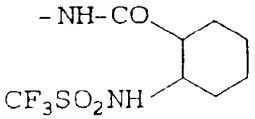
a group represented by formula:



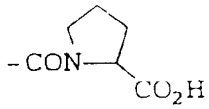
a group represented by formula: -NHCO$(CH^2)_t$COOH (wherein t represents 1 to 3);
a group represented by formula: -NHCOCH=CH-CO_2H;
a group represented by formula: -$NHCOCH_2CH(Ph)CO_2H$;
a group represented by formula: -$NHCOCH(Ph)CH_2CO_2H$;
a group represented by formula:



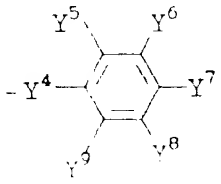
a group represented by formula:



a group represented by formula: -$CONHCH(Ph)CO_2H$;
a group represented by formula:

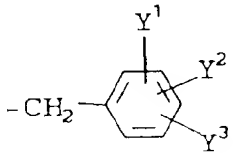


a group represented by formula: -$NHCOC(Ph)=C(Ph)CO_2H$;
phthalimido;
benzyloxy;
a mono- or dialkylamino having 1 to 4 carbon atoms;
acetoxy; or,
propionyloxy;
Y^3 represents:
hydrogen; or,
a group represented by general formula:

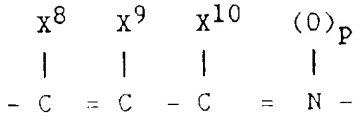


(wherein Y^4 represents a single bond; oxygen atom; sulfur atom; carbonyl group;
a group of formula: -NH-;
a group of formula: -CH = CH-
a group of general formula: $-N(Y^{10})CO-$ (wherein Y^{10} represents hydrogen, methyl or phenyl);
a group of general formula: $-CON(Y^{11})-$ (wherein Y^{11} represents hydrogen, methyl or phenyl);
a group of formula: $-CH_2NH-$;
a group of formula: $-NHCH_2-$;
a group of general formula: -CH2-Y^{12}- (wherein Y^{12} represents oxygen or sulfur);
a group of general formula: $-Y^{13}-CH_2-$ (wherein Y^{13} represents oxygen or sulfur); or,
a group of formula: -NHCONH-;
each of Y^5, Y^6, Y^7, Y^8 and Y^9 independently represents an alkyl group having 1 to 4 carbon atoms, halogen, carboxyl, carbamoyl, hydroxy, methoxy, ethoxy, mercapto, methylthio, ethylthio, sulfo, sulfamoyl, nitro, trifluoromethanesulfonylamino, methanesulfonylamino, benzenesulfonylamino, 4-chlorobenzenesulfonylamino, acetylaminosulfonylmethy, methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl, amino, formyl, phospho, phosphono or cyano)).

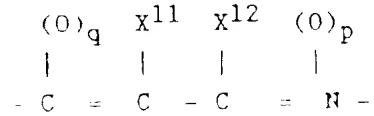
3. The composition for the prevention or treatment of hyperuricemia as claimed in claim 2, wherein:
Z^1 represents nitrogen atom;
Z^2 represents a group represented by general formula: $-C(X^2)=$;
Z^3 represents a group represented by general formula: $-C(X^3)=$; and,
Y represents a group represented by general formula:



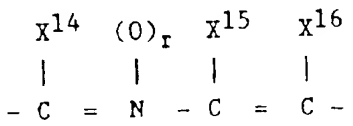
4. The composition for the prevention or treatment of hyperuricemia as claimed in claim 2, wherein:
Z^1 represents nitrogen atom;
Z^2 represents a group represented by general formula: $-C(X^2)=$;
Z^3 represents a group represented by general formula: $-C(X^3)+$; and X^2 and X^3 may be combined together to form:
a group represented by general formula:



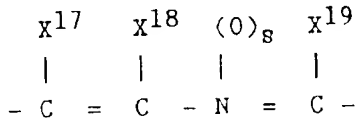
a group represented by general formula:



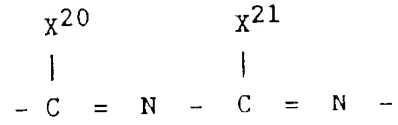
a group represented by general formula:



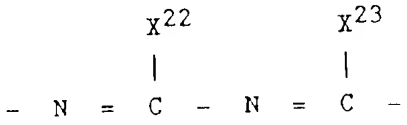
a group represented by general formula:



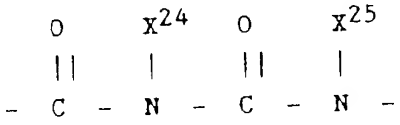
a group represented by general formula:



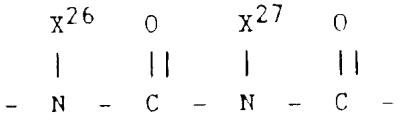
a group represented by general formula:



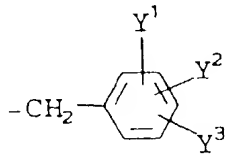
a group represented by general formula: or



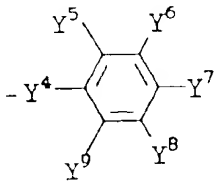
a group represented by general formula:



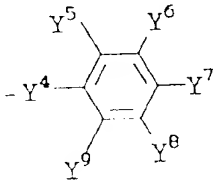
and,
Y represents a group represented by general formula:



5. The composition for the prevention or treatment of hyperuricemia as claimed in claim 3, wherein Y^3 represents a group represented by general formula:



6. The composition for the prevention or treatment of hyperuricemia as claimed in claim 4, wherein Y^3 represents a group represented by general formula:



7. The composition for the prevention or treatment of hyperuricemia as claimed in claim 5, wherein Y^4 represents a single bond; and Y^5 represents carboxyl group or tetrazolyl group.

8. The composition for the prevention or treatment of hyperuricemia as claimed in claim 6, wherein Y^4 represents a single bond; and Y^5 represents carboxyl group or tetrazolyl group.

9. The composition for the prevention or treatment of hyperuricemia as claimed in claim 2, wherein the compound of formula I is 2-butyl-4-chloro-5-hydroxymethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole.

10. The composition for the prevention or treatment of hyperuricemia as claimed in claim 2, wherein the compound of formula I is 5,7-dimethyl-2-ethyl-3-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-3H-imidazo[4,5-b]pyridine.

11. The composition for the prevention or treatment of hyperuricemia as claimed in claim 2, wherein the compound of formula I is 2-butyl-4-chloro-5-hydroxymethyl-1-[(2'carboxybiphenyl-4-yl)methyl]imidazole.

12. The composition for the prevention or treatment of hyperuricemia as claimed in claim 2, wherein the compound of formula I is 5,7-dimethyl-2-ethyl-3-[(2'carboxybiphenyl-4-yl)methyl]-3H-imidazo[4,5-b]pyridine.

13. The use of a non-peptide compound having angiotensin II receptor-antagonizing activity for the preparation of a medicament for the treatment of hyperuricemia.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number

EP 91 30 9176

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
Y	THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 252, no. 2, 1990, pages 726-732, The American Society for Pharmacology and Experimental Therapeutics, US; P.C. WONG et al.: "Nonpeptide angiotensin II receptor antagonists. IX. Antihypertensive activity in rats of DuP 753, an orally active antihypertensive agent" * Entire document * ---	1-13	A 61 K 31/415 A 61 K 31/44
D,Y	DRUG NEWS & PERSPECTIVES, vol. 3, no. 6, July 1990, pages 337-351; A.L. JOHNSON et al.: "Nonpeptide angiotensin II receptor antagonists" * Pages 337-338; figures 8,18; "Conclusion" * --- -/-	1-13	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5) A 61 K

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims

Claims searched completely :

Claims searched incompletely : 1-8

Claims not searched :

Reason for the limitation of the search:

see sheet -C-

Place of search	Date of completion of the search	Examiner
THE HAGUE	19-03-1992	KLAVER T.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number EP 91 30 9176

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
Y	THE AMERICAN JOURNAL OF MEDICINE, vol. 44, no. 3, March 1968, pages 359-365; T.F. FERRIS et al.: "Effect of angiotensin and norepinephrine upon urate clearance in man" * Page 363: "Comments" * ---	1-13	
Y	JOURNAL OF THE AMERICAN GERIATRICS SOCIETY, vol. 26, no. 6, June 1978, pages 241-247; I. SAITO et al.: "Serum uric acid and the renin-angiotensin system in hypertension" * Abstract; discussion * ---	1-13	
A	BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 165, no. 1, 30th November 1989, pages 196-203, Academic Press, Inc.; A.T. CHIU et al.: "Identification of angiotensin II receptor subtypes" ---		TECHNICAL FIELDS SEARCHED (Int. Cl.5)
D,A	HYPERTENSION, vol. 15, no. 3, part 2, June 1990, pages 841-847; J.P. KOEPKE et al.: "Central and peripheral actions of a nonpeptidic angiotensin II receptor antagonist" ---		
A	MEDIZINISCHE KLINIK, vol. 69, no. 14, 5th April 1974, pages 599-606; F. WESSELS et al.: "Untersuchungen zur Genese der hyperurikämie bei essentieller hypertonie" -----		

EP 91 30 9176 -C-

In view of the large number of compounds defined by the general formula of claims 1-8 the search has been limited to the inventive part of the molecule and/or the compounds mentioned in the description and/or the compounds mentioned in the claims.

(PCT Art. 6; EPC Art. 84; Guidelines for examination in the European Patent Office, Part B, Ch. II.7 and III.7)

Meaningful search not possible on the basis of all claims:

Claims 1-12 were read as being second-use claims.